NMRDCINST 3900.2
NMRDC:04B
7 Jun 1993

From: Commanding Officer, Naval Medical Research and Development Command

Subj: PROTECTION OF HUMAN RESEARCH VOLUNTEERS FROM RESEARCH RISKS

Ref: (a) SECNAVINST 5212.5C, “Navy and Marine Corps Records Disposition Manual”
(b) SECNAVINST 5211.5D, “Department of the Navy Privacy Act (PA) Program”
(c) CNO ltr Ser 093/2U239066 of 10 Mar 92
(d) OPRR Reports “Policy on Informing Those Tested About HIV Serostatus” of 10 Jun 1988
(e) OPNAVINST 5300.8A “Coordination and Control of Personnel Surveys,” of 16 Jan 1984

Encl: (1) SECNAVINST 3900.39B, “Protection of Human Subjects”
(2) DoD Directive 3216.2, “Protection of Human Subjects in DoD-Supported Research,”
(3) DoD Regulation, “Protection of Human Subjects,” (Title 32 Code of Federal Regulations Part 219) of 19 Aug 1991
(4) NAVMEDCOMINST 6710.4, “Use of Investigational Agents in Human Beings”
(5) FDA Regulation, “Investigational New Drug Application,” (Title 21 Code of Federal Regulations Part 312.2) of 1 Apr 92
(6) Belmont Report - The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1979
(7) Format for Research Protocols
(8) Sample Consent Form
(9) Sample Privacy Act Statement
(10) Format for Investigator Assurance Agreement
(11) Format for Committee for the Protection of Human Subjects Recommendation
(12) Format for Committee for the Protection of Human Subjects Recommendation - Continuing Review

1. Purpose. This instruction supplements references (a) through

(e) and enclosures (1) through (12), provides additional guidance, and establishes Naval Medical Research and Development Command (NAVMEDRSCHDEVCOM) policies for the protection of human research volunteers.

2. Scope. This instruction applies to all research involving research volunteers conducted, supported or otherwise subject to regulation by NAVMEDRSCHDEVCOM. Specifically:

a. The provisions of this instruction apply to:

(1) All studies, regardless of funding source, conducted at, by or in collaboration with any NAVMEDRSCHDEVCOM activity. Studies include preliminary activities (e.g. calibration of equipment and collection of pilot data) that precede the main data collection effort.

(2) Contract research funded by NAVMEDRSCHDEVCOM.

b. This instruction does not apply to research activities that meet the requirements for exemption from compliance with enclosures (1), (2) and (3), inclusively.

c. Nothing in this instruction is intended to limit the authority of a health care practitioner to provide emergency medical care under applicable law of the jurisdiction in which the care is provided.

d. Except as specifically indicated, nothing in this instruction is intended to limit the authority of unit commanders in the discharge of assigned duties or responsibilities.

3. Policy. Responsibility for the protection of research volunteers is a Command responsibility involving all hands. In all work governed by this instruction, the welfare of research volunteers is considered preeminent and, along with full compliance with applicable regulations and Command policy, takes precedence over specific research programs. These requirements for protection of research volunteers are minimum standards. While waiver of certain requirements of these regulations may decrease the cost, difficulty, or political or social complexity of performing a study, these reasons alone do not offer sufficient justification to waive protections afforded the research volunteer.

4. Background. Over the years, successive international declarations have been formulated that define the conditions under which humans may be used as subjects in research. The first attempt to

set international standards was the Nuremberg Code of 1947. This Code was an outgrowth of the Nuremberg Trials of war criminals who performed experiments on prisoners and detainees during the Second World War. The Nuremberg Code was followed in 1964 by the Declaration of Helsinki, which was itself revised in 1975 at the 29th World Medical Assembly. The most recent internationally recognized document is the Proposed International Guidelines for Biomedical Research Involving Human Subjects, which was produced in 1982 as a joint project of the World Health Organization and the Council for International Organizations of Medical Sciences. This document is currently under revision. An important historical document in the United States is the Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, produced by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979 (enclosure (6)). The three basic ethical principles discussed in the Belmont Report - respect for persons, beneficence and justice - guide the ethics of research involving human volunteers. The essential elements in the protection of human research volunteers are: review of the research protocol by a Committee for the Protection of Human Subjects (Institutional Review Board, or other designation); determination that the benefits from the research outweigh the risks; approval of the protocol; implementation of all reasonable safety measures and means to reduce risk to research volunteers; provision of an easily accessible point of contact for research volunteers' rights and for care in case of research-related injury; and provision of informed voluntary consent by each research volunteer. These principles and procedures are the foundation upon which this instruction is based.

5. Delegation of Authority.

a. Enclosure (1) assigns the Director of Naval Medicine/ Surgeon General of the Navy (DNM/SG) approval authority for all Navy studies using research volunteers that do not require approval by the Assistant Secretary of the Navy (Research, Engineering and Systems) (ASN(RE&S)). [N.B. The designation of ASN(RE&S) has been changed to Assistant Secretary of the Navy (Research, Development and Acquisition) (ASN(RD&A)). This latter designation will be used in this instruction.]

b. The DNM/SG has delegated approval authority to a medical or dental officer assigned to Naval Health Sciences Education and Training Command for studies involving research volunteers that are supported by the Navy Clinical Investigation Program (CIP) and do not require ASN(RD&A) approval.

c. The DNM/SG has delegated approval authority to a medical

or dental officer assigned to NAVMEDRSCHDEVCOM for studies involving research volunteers that are supported by NAVMEDRSCHDEVCOM, do not require ASN(RD&A) approval, and which are not part of the CIP.

d. The DNM/SG has delegated to Commanding Officers of NAVMEDRSCHDEVCOM laboratories, approval authority for studies involving research volunteers conducted by their respective Commands and Detachments, providing that these studies involve no greater than "minimal risk" (reference (c)). "Minimal risk" is defined in enclosure (1).

e. In all cooperative and contract research, the cooperative research plan or contract, as appropriate, will clearly define the responsibility and authority of all parties such that the requirements for the protection of research volunteers will not be diminished.

6. Conflicting Regulations. Issues pertaining to the protection of human volunteers participating in research are in a state of evolution. This may result in confusion and apparent conflict in the applicable regulations. NAVMEDRSCHDEVCOM personnel are instructed that:

a. Enclosure (3) carries the force of law and supersedes administrative regulations (enclosures (1) and (2) and references (a) through (d)).

b. In all cases, the regulation offering the greatest protection for the research volunteers will prevail. This includes regulations cited as enclosures (1) through (5) and references (a) through (c); this instruction; institutional regulations; local, state and Federal laws and regulations; and, where applicable, foreign laws and regulations.

c. In the event of significant conflict between regulations, requests for guidance should be forwarded to NAVMEDRSCHDEVCOM.

7. Research Protocols.

a. For each study involving research volunteers, a research protocol will be prepared that fully describes the proposed study. The content and format of the protocol are outlined in enclosure (7). Deviation from this format is authorized provided the protocol contains the requisite information to fully describe the study and its attendant risks.

b. The protocol will describe how appropriate anonymity will

be maintained for any human samples or identifiable data collected or used.

c. The research protocol will contain a determination of the adequacy of the proposed sample size. This will be in the form of a statistical power calculation stated in terms of the hypothesis to be tested, or by other appropriate means. Calculations will be reviewed by the Committee for the Protection of Human Subjects (CPHS) for the appropriateness of exposing research volunteers to research risks relative to the likelihood that the research results will adequately address the hypotheses under test. In the event that sample size calculations are not warranted, explanation for omitting this aspect of the research protocol will be stated for review and consideration by the Committee.

d. The protocol will describe each study or procedure to be performed.

(1) For each procedure or study, the protocol will include:

(a) a brief description of the procedure;

(b) a list of the most significant risks;

(c) the safeguards in place to minimize risk and deal with emergencies;

(d) a list of the total number of volunteers to be enrolled, whether military or civilian, male or female, and the age range of volunteers (the proposed number of human subjects that will be used in the studies must be specific); and

(e) justification to show that studies in animals or <u>in vitro</u> systems could not address the hypothesis(es) under test.

(2) Procedures that will be performed by other than NAVMEDRSCHDEVCOM institutions must have attachments showing an agreement by that institution to only use qualified personnel to perform the procedure. This agreement must include the dates of the planned study.

e. For each research protocol, a single appropriately qualified medical monitor (i.e. physician or dentist, military or civilian) will be designated by name. This individual will be someone other than the principal investigator.

(1) The medical monitor is to be the individual responsible for medical monitoring of the study.

(2) The medical monitor has the authority and responsibility to terminate exposure of research volunteers to research related risks whenever termination of exposure is medically indicated.

(3) The primary qualifications and experience of the medical monitor, and of each individual to whom medical monitor responsibility will be delegated, must be determined to be sufficient to meet all requirements for the safe conduct of the study.

(4) The designated medical monitor responsible for a research protocol may, on occasion (or as a part of a watch standing bill), delegate specific authority to other qualified medical monitor(s) if he or she is not able to be present at a given time.

(5) In the absence of the medical monitor, the most senior military member and civilian staff member present will act in the place of the medical monitor to terminate exposure of research volunteers to research related risks whenever termination of exposure is considered in the best interest of the research volunteer.

(6) The principal investigator will ensure that any change of the medical monitor for an approved study will be reported to the CPHS, and will submit the qualifications of the replacement medical monitor to the CPHS for review.

(7) The designated medical monitor will ensure that the replacement medical monitor will be briefed regarding pertinent situations in the study to date. Formal transfer of responsibilities will be acknowledged in the form of a signed memorandum which will be filed in Appendix D of the protocol.

(8) In the event that a study does not warrant a medical monitor, a request for waiver of this requirement is to be forwarded to the appropriate authority in accordance with paragraph 22 of this instruction.

f. For studies that involve minors or third party permission, and are conducted outside the legal jurisdiction of the United States, the research protocol will state the age of majority and the legal requirements for third party permission for the country, state or area in question. In addition, the protocol will describe how the requirements of paragraph 8.d. are met.

g. For each protocol, the principal investigator will attach a cover letter when the protocol is initially submitted and when significant modification of the protocol is requested. The letter will clearly and completely describe any special circumstances for consideration, request for waiver or exemption from compliance with regulations (state requirement and reason for requested deviation), and any other issues that will assist the CPHS in assessing the merit and acceptability of the protocol. The letter will include the location (page and paragraph numbers) of the elements for consideration in the protocol.

8. Voluntary Informed Consent.

a. Voluntary informed consent will be obtained for all NAVMEDRSCHDEVCOM sponsored research. The elements of the informed consent process are detailed in enclosure (1).

b. Whenever possible, written informed consent (as demonstrated by a signed consent form) will be obtained. If it is not possible to obtain written informed consent, a waiver of this requirement may be requested in accordance with paragraph 22 of this instruction. This request for waiver must be clearly documented and justified in the protocol. Provided that the described voluntary informed consent process meets the requirements of applicable guidance and the research exposure involves no more than minimal risk to the volunteer, waiver of the requirement for obtaining a signed consent form (but not waiver of the consent process itself) may be granted by the approving authority. In all cases where the requirement for a signed consent form has been waived, investigators will document the consent process in writing in accordance with the requirements of enclosure (1), paragraphs 7.d. through 7.g.. Waiver of the requirement to obtain a signed consent form in research involving research volunteers is not meant to be a routine procedure.

c. Except as noted below, individual voluntary informed consent of each research volunteer is required. While it may be necessary to also obtain permission from a third party to conduct a study, especially in foreign locations, third party permission by itself is not sufficient to meet the requirements of these regulations.

d. The one exception to the requirement for individual voluntary informed consent is legally sufficient third party permission, as in the case of a minor, or an incapacitated individual unable to give informed consent. Where third party permission is employed:

(1) Investigators are required to inform the actual participant in the research protocol about the procedures and implications of participation. This will be done to the extent that the participant is capable of understanding and to the extent that it is in the best interest of the participant. Comment will be made by the investigator in the protocol concerning the intent of the investigator to provide information to the individual participant for whom third party permission is obtained.

(2) The CPHS will consider and determine whether the assent of the actual participant is required for participation of that individual in the study. This determination and recommendation will be reflected in the minutes of the CPHS meeting.

e. If “third party permission” is given by the parent of a minor or the legal guardian, next-of-kin, or other legally authorized third party representative of any individual, the following conditions must be met:

(1) the prospective participant in the research must be legally incapable of giving informed consent;

(2) the measures to be used in the research must be intended to be beneficial to the participant;

(3) investigators must demonstrate that the individual providing permission is legally authorized to do so; and

(4) the permission is legally effective in the locale where it is obtained and the research exposure of the participant takes place.

f. The consent form will provide names and telephone numbers or other appropriate means of contact for the principal investigator and medical monitor in the event that the research volunteer has a question that arises during or after the course of the study.

g. Foreign national volunteers and volunteers who are not fluent in the English language will be provided the informed consent process in their native language. All consent forms used must have an accurate and complete translation of the English version into the appropriate foreign language. This translation will be an integral part of the protocol and will be submitted with the original protocol for review. Willful failure to provide and use an accurate and complete translation will result in disapproval or termination of the research.

h. A sample consent form is provided as enclosure (8).

9. Committee for the Protection of Human Subjects.

a. Proposed studies involving research volunteers will be reviewed by a Committee for the Protection of Human Subjects (CPHS). This committee may be synonymously referred to as the Review Committee, Human Subjects Committee, or Institutional Review Board. The Committee for the Protection of Human Subjects is the preferred terminology.

b. The term of Committee members will be generally for a period of two (2) years. Appointments should be staggered to ensure continuity.

(1) By the first day of each fiscal year (1 October) the convening authority of each NAVMEDRSCHDEVCOM CPHS will forward to NAVMEDRSCHDEVCOM a list of all CPHS members for that fiscal year. This list will indicate the Chairperson, Alternate or Co-Chairperson, and the representation of each Committee member (e.g. physician, attorney, clergy, medical ethicist, officer, enlisted, civilian, community representative, etc.).

(2) Changes to the Committee occurring during the fiscal year will be reported to NAVMEDRSCHDEVCOM as they occur.

c. A quorum of at least five members of the CPHS who are eligible to vote on a specific research protocol will be required to convene a meeting and consider action on that protocol. The voting members of the CPHS reviewing the specific research protocol must include:

(1) at least one member whose primary concerns are in scientific areas;

(2) at least one member whose primary concerns are in nonscientific areas; and

(3) at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

An individual member of the CPHS may simultaneously fulfill more than one of the above criteria.

d. The determination of the CPHS will be made by majority vote. Voting by CPHS members will be recorded anonymously. The

recommendation document will state the count of the vote for approval or disapproval.

e. A CPHS convened at a foreign location will have at least one member appointed to the Committee by the convening authority as a representative of the host government. This representative will be: a non-voting member of the CPHS; designated by the appropriate agency of the host government; and a national employee of the host government. This representative may not be an employee, contractor or otherwise affiliated with the NAVMEDRSCHDEVCOM activity such that there would be a conflict of interest. The host government representative is authorized to participate in all Committee deliberations pertaining to studies conducted in the host country or involving host country nationals.

f. The convening authority may appoint consultants to the CPHS to supplement technical expertise required in a field that is not adequately represented by the CPHS members present and eligible to vote on a specific research protocol. These consultants may be excluded from Committee deliberations, at the discretion of the Chairperson of the CPHS, and are neither eligible to vote nor to be considered in determining the presence of a quorum.

10. Basic Review and Approval Procedures. The basic procedures for review and approval of human research protocols within NAVMEDRSCHDEVCOM are outlined below. Contractors funded by NAVMEDRSCHDEVCOM or its subordinate activities will ensure that their respective institutional review mechanisms comply with the intent of these procedures.

a. Research protocols will be submitted for each study involving research volunteers in the format provided in enclosure (7) or equivalent. If a particular element is not applicable to a given research protocol, the principal investigator will enter “N/A” or otherwise provide justification why the element is omitted.

b. Approval within NAVMEDRSCHDEVCOM of protocols involving research volunteers will be based upon a tiered review process.

(1) Studies involving no more than minimal risk will be reviewed by the laboratory Command or Detachment CPHS and will be approved by the laboratory Commanding Officer. Oversight and review responsibility for this process will be exercised by NAVMEDRSCHDEVCOM.

(2) Studies involving greater than minimal risk will be reviewed by the laboratory Command or Detachment CPHS and will be

forwarded to NAVMEDRSCHDEVCOM for approval, along with the recommendation of the convening authority and the laboratory Commanding Officer, if applicable. The convening authority is the Commanding Officer at a performing NAVMEDRSCHDEVCOM Command, or the Officer in Charge at a performing NAVMEDRSCHDEVCOM Detachment. Protocols will be reviewed at NAVMEDRSCHDEVCOM in one of two ways:

(a) Complicated studies, those involving significant risk to the volunteer, or those involving significant ethical or legal issues will be reviewed by a NAVMEDRSCHDEVCOM CPHS constituted and functioning in accordance with this instruction and higher guidance. If acceptable, the research protocol will be approved by the Commanding Officer, NAVMEDRSCHDEVCOM or other official specifically designated by the Commanding Officer to approve research involving research volunteers.

(b) Uncomplicated studies in which the risk to the volunteer is not great and is clearly outweighed by the benefit of the research will be reviewed by a three person panel constituted by the Commanding Officer, NAVMEDRSCHDEVCOM and chaired by the Chairperson of the NAVMEDRSCHDEVCOM CPHS. If acceptable, the research protocol will be approved by the Commanding Officer, NAVMEDRSCHDEVCOM or other official specifically designated by the Commanding Officer to approve research involving research volunteers.

(3) Requests for special handling (e.g. processing for approval in a time frame more rapid than possible under normal working conditions) should be addressed to the Commanding Officer, NAVMEDRSCHDEVCOM.

c. The Commanding Officer or Officer in Charge of the performing NAVMEDRSCHDEVCOM activity has the responsibility to establish a scientific review process that ensures that proposed research has sufficient merit to warrant exposing research volunteers to research risks. This review is normally conducted by a committee having the title “Scientific Review Committee” or similar designation. The following comments pertain:

(1) Simultaneous assignment of an individual to membership on both the “Scientific Review Committee” and the CPHS should be minimized to the greatest extent possible.

(2) The purpose and function of the CPHS will not be combined with the purpose and function of a “Scientific Review Committee”.

(3) The CPHS may make recommendations generally considered to fall within the purview of the "Scientific Review Committee" to the extent that these recommendations pertain to considerations for the protection of research volunteers.

d. It is the responsibility of the CPHS convening authority and the Chairperson of the CPHS to ensure that research protocols are reviewed and evaluated in strict compliance with all elements of pertinent laws, regulations, and NAVMEDRSCHDEVCOM guidance.

(1) It is the responsibility of the convening authority to establish a timetable for submission and review of research protocols.

(2) If a principal investigator submits a protocol for review and requests action from the CPHS in less than the routinely allotted time, the principal investigator will provide justification for the request. The Chairperson, CPHS may accept the submission for special review, or deny the request for special handling and treat the protocol as a routine submission. The principal investigator will be informed of the decision.

(3) If the CPHS can not complete action on a protocol in the time designated by the convening authority, the Chairperson of the CPHS will inform the principal investigator of the reason for the delay and the expected completion date for Committee action.

(4) The principal investigator and Chairperson, CPHS will provide copies of the request for special handling, decision on the special handling request, and notification of delay in completion of CPHS action to the convening authority.

e. Expedited review, as defined in paragraph 5.q. of enclosure (1), is not authorized.

f. No member of the CPHS will vote upon or participate in the review of a research protocol in which he or she is materially involved or has a conflict of interest. Material involvement or conflict of interest includes managerial or leadership responsibility for the research protocol under review, principal or co-investigator status, or other conflicts of interest as determined by regulation or by the convening or approving authority. Persons with conflicts of interest may only be present at meetings during the time that they are providing information requested by the CPHS. Presence during the discussions or deliberations of the CPHS is not authorized.

g. If the CPHS convening or approving authority for a research protocol is involved as a principal or co-investigator for the protocol, or if any other conflict of interest exists, that individual is disqualified from taking official action. The protocol and all pertinent documents will be forwarded to the next higher echelon in the chain of command for action, along with a statement indicating the reason for disqualification.

h. Certain research protocols may be exempt from CPHS review:

(1) Enclosures (1) and (3) list categories of research which are exempt from policies and regulations pertaining to protection of research volunteers. It is the responsibility of the CPHS convening authority to ensure that exemptions are properly reviewed and justified in relation to both enclosures (1) and (3) prior to initiation of the study.

(2) If there is any question whether a specific research protocol is exempt from review, the protocol is to be considered non-exempt and receive a full review.

(3) No research protocol involving children or fetal-related research will be exempt from CPHS review. In such cases, full review is required.

(4) If a research protocol is determined to be exempt from review, a statement is required indicating the criteria for exemption and the authority by which exemption is claimed. The exemption statement must be signed by the Chairperson, CPHS, and the convening and approving authorities.

i. Investigators are required to provide sufficient detail in the research protocol so that members of the CPHS and other reviewers will have a clear and complete understanding of all work that is to be performed under the protocol. Failure to provide necessary detail will result in return of the protocol for revision, or result in disapproval.

j. All aspects of the welfare of a research volunteer related to his or her participation in a study will be considered as directly relevant to the issue of protection of research volunteers when a research protocol is reviewed. The following comments pertain:

(1) The exact role of NAVMEDRSCHDEVCOM investigators or contractors in clinical decision making or therapeutic intervention will be specified in the research protocol.

(2) NAVMEDRSCHDEVCOM and subordinate activities will evaluate all proposed research to ensure that both the experimental exposure and related medical care a research volunteer may receive as an integral part of the study are scientifically, medically, legally and ethically appropriate and correct.

(3) Review of research protocols will evaluate pertinent aspects of the research volunteers' proposed experimental exposure and related medical care, assess the ability of the medical system outlined in the research protocol to provide that medical care, assess the qualifications of the health care providers, and evaluate any other pertinent factors relating to the welfare of the volunteer.

(4) If any element of the protocol is found to be unacceptable, then consideration of the welfare of the research volunteer will preclude approval of or participation in the study unless all deficiencies are corrected.

k. Unless a research protocol is deemed exempt from review (as specified in both enclosures (1) and (3)), review and approval of the protocol must be completed prior to either enrollment of any research volunteers, or collection or use of data or specimens derived from research volunteers. Local policy documents will clearly state that non-exempt research involving research volunteers will be reviewed by the CPHS, regardless of perceived risk to research volunteers. It is the responsibility of Commanding Officers and Officers in Charge of the performing or funding NAVMEDRSCHDEVCOM activity to ensure these policies are known and followed throughout their commands.

l. The minutes of the CPHS will be forwarded to the approving authority, along with any recommendation for action by the convening authority. For each protocol, the minutes should anonymously reflect the Committee discussion. Minutes of the CPHS meetings will be in sufficient detail to show attendance at the meetings; actions taken by the CPHS; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of discussion of controversial issues and their resolution. The minutes will include anonymous statements describing the reason(s) for each vote to disapprove or abstain from voting. These minutes will be retained indefinitely in the research protocol.

m. Upon review of a research protocol, in accordance with

enclosures (1), (2), (3), this instruction and other applicable laws and regulations, the CPHS will determine a level of risk to research volunteers and make a recommendation to the convening and approving authority whether a specific research protocol should be approved, approved with minor changes expressly specified by the CPHS, or disapproved. This recommendation will follow the format provided as enclosure (11).

n. Original signatures are required on all documents pertaining to the protection of research volunteers (research protocols, consent forms, review and approval documents, etc.). Photocopies and facsimile copies of signatures may be accepted for processing of documents and granting specified limited time approval to conduct research. Such temporary approvals will be authorized by the approving authority for a reasonable period of time necessary to obtain original signed documents. It is the responsibility of the principal investigator to obtain original signatures on the research protocol and Investigator Assurance Agreement from all co-investigators and from the responsible department head or equivalent. The principal investigator is also responsible for ensuring that consent forms are properly signed by each research volunteer (or the research volunteer's legally authorized representative), an investigator, and a witness. The Chairperson, CPHS is responsible for obtaining original signatures of all committee members participating in the review of a given research protocol. The format for the Investigator Assurance Agreement is provided as enclosure (10).

o. Specific review for legal sufficiency is required for research protocols where third party consent is necessary (paragraph 7.h. of enclosure (1)). Final approval will be based upon the balance of risks to research volunteers and benefits of the study to the research volunteer. This review must be appropriately noted in the minutes of the CPHS meeting.

p. The CPHS will review Investigator Assurance Agreements for compliance with the format provided as enclosure (10).

(1) The CPHS will ensure that all investigator(s) signatures are provided on the Agreement. Failure of the principal investigator to present an Agreement with all required signatures may result in return of the research protocol without action.

(2) The CPHS may consider a protocol without a completed Investigator Assurance Agreement if the principal investigator provides an explanation why the necessary signatures are not included, as well as a timetable for obtaining the signatures.

(3) No investigator may participate in any way in non-exempt research involving research volunteers, or in the collection or use of data or specimens derived from such research volunteers, prior to completion of the Investigator Assurance Agreement.

q. The CPHS will review each research protocol to determine if there is a research collaboration with an investigator or institution outside of the Command responsibility of the approving authority. In all cases where outside collaboration exists, the CPHS either will require inter-institutional or inter-agency cooperative research plans in which arrangements are made to avoid duplication of effort in the review process, or will require review and approval by the Committees for the Protection of Human Subjects of all the collaborating institutions in accordance with Department of Defense and Navy regulations (see paragraph 12.).

r. After review of a research protocol, the CPHS may: recommend approval of the protocol; recommend approval with explicit requirements for minor revision; return the protocol directly to the submitting investigator for specific major revision; or recommend that the protocol not be approved. If a protocol is returned to the submitting investigator with recommendation for approval with minor revision, the following procedures will be followed:

(1) The minutes of the CPHS will describe in exact and complete detail the requirements for the revision.

(2) If the protocol is revised by the submitting investigator exactly as described in the detailed requirements recorded in the minutes of the CPHS, the Chairperson may review these changes for compliance and, if correct and complete, forward the revised protocol as being recommended for approval by the CPHS. Further consideration by the full Committee is not required. This is not considered expedited review.

(3) The Chairperson reviewing the minor revisions will attach a memorandum indicating that the revisions to the protocol satisfy <u>all</u> requirements for revision determined by CPHS review.

(4) If after review of the submitted revisions, the Chairperson believes that the revised protocol should be resubmitted for full Committee review, he or she is authorized to do so.

(5) Failure of the submitting investigator to satisfy all revision requirements as noted in the minutes of the CPHS, or the addition, deletion or change of any other element in the protocol, will necessitate reconsideration of the revised protocol by the

full Committee.

(6) It is the responsibility of the principal investigator alone to submit a revised protocol for review of modifications as discussed above.

(a) Revisions to the protocol will include a signed statement from the principal investigator certifying that he or she has informed all co-investigators about the changes to the protocol and all co-investigators agree to accept and abide by the changes. All co-investigators contacted must be listed by name.

(b) Demonstration of acceptance of the revisions by the signatures of co-investigators is strongly encouraged.

(c) Lack of documentation of agreement by all co-investigators will preclude acceptance of the revisions by the CPHS and approving authority.

(7) Use of the procedures described in this section is at the discretion of the CPHS. If used, the specific acceptance of this process by the CPHS at the time of initial consideration or review of the protocol is required. This process is meant to be used for minor revisions. If required changes are major or complex, these procedures are not to be used. In such cases, a revised protocol will be submitted for full review.

(8) If a principal investigator desires to modify an already approved protocol such that the changes are within the parameters of the approved experimental design (e.g. withdraw a 5 cc blood specimen volume instead of the approved 10 cc specimen volume, exercise a volunteer for 10 minutes at the approved exercise intensity instead of 15 minutes at that intensity, etc.), these changes may be made by the principal investigator without submission of the protocol to the CPHS for additional review. A record of such changes must be made in the protocol.

s. The recommendation of the CPHS will be forwarded to the approving authority with the dated signature and typed name, business address and representation of each CPHS member present at the meeting, and the dated signature of the convening official of the activity.

t. Upon approval, the recommendation document will state the CPHS assessment of the level of risk of the proposed research protocol, indicating that it is either:

(1) of minimal risk as defined by enclosures (1) and (3);

(2) of more than minimal risk but does not require ASN(RD&A) approval according to paragraph 12 of enclosure (1); or

(3) requires ASN(RD&A) approval.

u. For purposes of review and approval of research protocols involving multiple elements of varying risk, the entire protocol will be classified by the element of greatest risk.

v. Research protocols that are determined by the CPHS to involve only “minimal risk” may be approved by the Commanding Officer of the performing or funding NAVMEDRSCHDEVCOM activity. A complete copy of the approved protocol, including all supporting documents, will be forwarded to NAVMEDRSCHDEVCOM. This will be done upon initial approval and after each approval for continuation of the research.

w. Research involving more than “minimal risk” will be additionally reviewed at NAVMEDRSCHDEVCOM in accordance with this instruction and the requirements of higher authority.

x. Research protocols which require ASN(RD&A) approval must be submitted via the chain of command to the Chief of Naval Operations (N093 and N091) for forwarding to the ASN(RD&A). Correspondence must be endorsed initially by the Chief of Naval Personnel if Navy personnel will be subjects, or by the Commandant of the Marine Corps (ATTN: Chief of Staff for Manpower) if Marine Corps personnel will be subjects. Responsibilities of the via addressees are listed in enclosure (1). In all cases, the DNM/SG should be specifically asked to comment on the balance of medical risks and benefits to research volunteers.

y. The requirements for protection of research volunteers represent minimum standards. Any higher authority in the chain of command is authorized to disapprove a research protocol or apply additional restrictions to any protocol. Lessening of restrictions is not authorized. An assessment of risk, the requirement for the protection of research volunteers, or disapproval of a protocol may not be downgraded or superseded in the chain of command review. In no case may the approving authority approve research without the recommendation for approval of the reviewing CPHS and of its convening authority. In the event of a dispute, all relevant information is to be forwarded through the chain of command to NAVMEDRSCHDEVCOM for review and resolution.

z. Upon receipt of a research protocol forwarded with the recommendation of both the CPHS and the convening authority, the approving authority may:

(1) accept the recommendation of the CPHS;

(2) require additional safeguards or additional modifications to the protocol that enhance the protections afforded research volunteers;

(3) assign either a greater level of risk, protection from risk, or requirement for review to a protocol than has been assigned by the CPHS;

(4) require review of a protocol which the CPHS has determined to be exempt from review; or

(5) disapprove the protocol, despite the CPHS recommendation to approve the protocol.

11. Responsibility for Protection of Research Volunteers in Research Involving More than One Activity. Research involving more than one activity will either be reviewed at each activity independently, or a cooperative research plan will be established in which arrangements are made to avoid duplication of review effort. In all cases, standards for protection of research volunteers and requirements for compliance with governing regulations will be maintained.

a. For joint research programs, one activity will be designated as having primary responsibility. Primary responsibility for protection of research volunteers means ensuring compliance with the provisions of this instruction and its references and enclosures. The activity with primary responsibility must exercise that responsibility even during phases of the research carried out by other activities. Continuity of primary responsibility is necessary to avoid gaps in protection of research volunteers.

b. Paragraph E.3.b. of enclosure (2) provides guidance for studies involving more than one military Department or Agency (e.g. Army and Navy). A cooperative research plan, signed by the heads of the activities, will state which activity has primary responsibility.

c. When more than one Navy activity is involved, primary responsibility for protection of research volunteers depends upon whether the research volunteers are patients of a Navy Medical

Treatment Facility (MTF) or Dental Treatment Facility (DTF) as indicated below. A cooperative research plan, signed by the heads of the activities, will state which activity has primary responsibility.

(1) When the research, regardless of in-house or contract status, involves participation of patients of a Naval MTF/DTF, the MTF/DTF has primary responsibility, except as provided by enclosure (2).

(2) For research not involving patients at a Naval MTF/DTF, primary responsibility will be assigned in the written cooperative research plan, by agreement of the heads of activities.

d. The approving authority may agree to assign responsibility for review of issues related to protection of research volunteers to another authorized review and approving authority in the written cooperative research plan.

e. Review and approval by another approving authority, based on a written cooperative research plan, must meet all requirements of this instruction, including requirements of enclosures (1) through (5) and references (a) and (b).

f. Signature of the Investigator Assurance Agreement by each investigator is required. Documentation of individual institutional review and approval of the research is required for each institution unless an exemption or a joint review or other review arrangement applies. A given investigator may be exempt from these requirements if the work performed by that investigator is exempt from compliance with regulations for protection of research volunteers.

g. Concurrent or sequential review by multiple approving authorities may sometimes be required. In such cases, no changes to a NAVMEDRSCHDEVCOM approved research protocol are permitted without NAVMEDRSCHDEVCOM concurrence. If changes in a NAVMEDRSCHDEVCOM approved research protocol are required by another reviewing authority, the changes must be sanctioned by resubmission of the modified protocol through the NAVMEDRSCHDEVCOM approval process.

h. The primary NAVMEDRSCHDEVCOM CPHS must verify that the final protocol approved by the NAVMEDRSCHDEVCOM activity is the same protocol reviewed and approved by the non-NAVMEDRSCHDEVCOM approving authority(s). A specific statement to this effect is to be incorporated into the minutes of the CPHS meeting reviewing the protocol.

i. In the case of non-NAVMEDRSCHDEVCOM personnel conducting research under the auspices of NAVMEDRSCHDEVCOM activities (e.g. university personnel assigned to NAVMEDRSCHDEVCOM activities under Intergovernmental Personnel Act or other agreements), the NAVMEDRSCHDEVCOM activity will be the activity primarily responsible for protection of research volunteers. Formal agreements to minimize duplication of review efforts are encouraged. These should be a matter of concern in developing agreements for such personnel arrangements.

12. Selection of Research Volunteers.

a. Exclusion of individuals as research volunteers because of age, sex, race, ethnicity, or socioeconomic or military grouping, must be based upon a sound scientific or operational rationale. In cases of exclusion of a specific group, the following information is required as a part of the research protocol:

(1) exact criteria for the exclusion of individuals as research volunteers;

(2) scientific or operational requirements that necessitate the exclusion;

(3) potential effect on the individual member of an excluded group if the individual intended to be excluded is inadvertently enrolled and participates in the study; and

(4) potential effect on the research if the exclusion is not allowed.

b. The CPHS and convening and approving authorities will review each research protocol for appropriateness of restrictions based upon the information provided.

c. Pregnant women may not be involved as research volunteers in research covered by this instruction unless:

(1) the purpose of the research is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or

(2) the risk to the fetus is negligible (e.g., administration of questionnaires to pregnant women).

d. Non-pregnant women may participate as research volunteers

in the following circumstances:

(1) If there is no known, expected or potential risk to a pregnant woman, embryo or fetus should the woman be unknowingly pregnant or become pregnant during the course of the study, full participation as a research volunteer is allowed. The consent form will include a statement that there is no known risk to a pregnant woman, embryo or fetus in the event that the research volunteer is unknowingly pregnant or becomes pregnant during the course of the study. The consent form will also outline any risks or concerns, real or potential, to a female participating in the study.

(2) If there is a risk to either a potentially pregnant female research volunteer, embryo or fetus, the consent form will include a statement describing in detail the risks to a pregnant research volunteer, embryo or fetus in the event that the research volunteer is unknowingly pregnant or becomes pregnant during the course of the study. Prior to participation in the study, a clinical history must be obtained which indicates that the volunteer is unlikely to be pregnant. In addition, investigators must objectively demonstrate that the volunteer is not likely to be pregnant as described below:

(a) A negative urine human chorionic gonadotrophin pregnancy test is required prior to participation of the research volunteer in any potentially hazardous activity, or whenever the research volunteer, embryo or fetus is at risk due to an intervention based on participation in the study. The minimum requirements for the test are:

(1) the test must be sensitive enough to detect 25 milli-International Units per milliliter (mIU/ml) of human chorionic gonadotrophin (hCG), or less;

(N.B. This level of hCG <u>may</u> detect pregnancy as early as 10 to 12 days after conception, before the first missed menstrual period.)

(2) the test must be performed on the first voided urine sample collected on the day of the experimental exposure; and

(3) the test sample must be run with a positive and negative control.

(b) In cases where the adverse effects of experimental exposure in pregnancy warrant a higher degree of certainty that the female research volunteer is not pregnant, a negative serum

Beta human chorionic gonadotrophin (Beta-hCG) pregnancy test sensitive enough to detect 5 mIU/ml, performed in an appropriate laboratory, is required within 24 hours or less of participation of the research volunteer in any potentially hazardous activity, or whenever the research volunteer, embryo or fetus is at risk due to an intervention based on participation in the study. This test may detect pregnancy 1 to 2 days before the urine test described above.

(c) In cases where the adverse effects of experimental exposure in pregnancy warrant the highest degree of certainty that the female research volunteer is not pregnant, the experimental exposure should occur during the first ten days after the onset of menses (during the proliferative phase of the menstrual cycle). In such cases, consultation with a qualified obstetrician must be sought to determine the optimal laboratory studies available to confirm this phase of the menstrual cycle. A negative serum Beta-hCG pregnancy test is also required.

(d) The time interval between collection of a specimen for use in determination of pregnancy and the experimental exposure risk will be included in the permanent research records of the individual volunteer tested.

(e) Historical reports of sexual abstinence and use of contraception will not generally be considered acceptable substitutes for a documented negative pregnancy test in female research volunteers of childbearing potential.

(f) The research volunteer will be advised of risks associated with becoming pregnant during the course of the study. If she thinks that she may have become pregnant during the course of the study, she must be advised to report this to the medical monitor immediately. Statements to this effect will be included in the consent form.

(3) Requests for waiver of these requirements should be submitted in accordance with paragraph 22 of this instruction. Waiver may be granted in situations where the potential risk to the volunteer and her embryo or fetus is clearly outweighed by the expected benefit.

e. In research involving greater than minimal risk:

(1) The potential research volunteer must be either:

(a) an individual eligible for care at a military medical treatment facility (e.g. active duty member, retired mem-

ber, dependent of an active duty or retired member, Secretary of the Navy designee for health care benefits);

(b) a civilian employee of the U.S. Government for whom it has been determined that the Federal employees Workers' Compensation Program will be adequate to cover any injury or disability resulting from the employee's participation as a research volunteer; or

(c) an individual who will be afforded medical or health care benefits applicable to any potential injury or disability resulting from participation in the research protocol.

(2) Additional considerations may apply in cases where the potential research volunteer is a foreign national or a member of a foreign military organization. In such cases, however, the minimum requirements of paragraph 13.e.(1) must be met.

(3) The adequacy of the proposed health care benefits coverage for the potential research risks is an element for review by the CPHS. If coverage is not adequate, participation of the potential research volunteer in the research is not authorized.

(4) The reviewing CPHS will ensure that the consent form provides the research volunteer with complete information regarding any potential additional costs to the research volunteer that may result from participation in the research (e.g., insurance deductible or co-payment, administration costs, etc.).

f. Research done under contract will follow the same guidelines described in paragraph 12.e..

g. U.S. military personnel may participate as research volunteers. Consideration should be given to how participation affects readiness and availability to perform military duties. Additional reimbursement of the research volunteer for participation, monetary or otherwise, is prohibited except as specifically authorized by law or regulation. Special attention should be given to avoid any real or apparent coercion to participate as a research volunteer, especially in training contexts, or other situations associated with major career branch points.

h. Persons receiving medical care at military treatment facilities, such as active duty and retired military personnel and dependents, may participate as research volunteers in research related to their health care. Such persons may be compensated for these services when authorized by applicable directives. Retired

officers of a regular component are subject to limitations of 5 U.S.C. 5532.

i. No research involving prisoners or institutionalized mentally disabled persons serving as research volunteers will be permitted (enclosure (1), sections 8.k. and 8.l.).

13. Research Conducted Outside the United States. Research protocols that are conducted outside the jurisdiction of the United States require approval by the appropriate authorized official(s) of the host country government. The following comments pertain:

a. It is recognized that the process of obtaining host government approval may be time consuming. The CPHS and approving authority may, but are not required to, consider a protocol without host government approval.

b. Volunteers may not be allowed to participate in research without the required host government approval. Documentation of host government approval must be completed by the appropriate authorized officials of the host government and must state that:

(1) the host government is aware of the specific details of the research proposed;

(2) the host government concurs that it is appropriate research to be done in the host country;

(3) approval for involvement of host country national research volunteers is granted;

(4) the host government understands that the research will meet at least the minimum standards for the protection of research volunteers required by the U.S. Navy;

(5) the host government understands that it will receive a timely copy of all reports related to protection of human research volunteers including annual (or more frequent) reviews, and reports of any unanticipated problems involving risks to research volunteers; any serious or continuing noncompliance with requirements for protection of human research volunteers; or any suspension or termination of CPHS recommendation for approval of research; and

(6) the host government understands that it has the right to require any additional restrictions desired to ensure the protection of research volunteers.

c. It is the responsibility of the Chairperson, CPHS and the convening authority to ensure that host government approval is obtained from the appropriate level and branch of the host government, in accordance with host country law and practice. If no policies exist for obtaining such approvals, involved NAVMEDRSCHDEVCOM activities must actively seek to have the host government establish such policies.

14. Maintenance of Records. All records associated with a research protocol involving research volunteers will be maintained as directed in enclosure (1) and reference (a), and remain permanently retrievable by the performing or funding (in the case of contract work) NAVMEDRSCHDEVCOM activity.

a. It is the responsibility of the approving authority to ensure that records are maintained in accordance with reference (a).

b. If cooperative research is conducted in conjunction with a non-U.S. Navy activity, the agreement between the activities (cooperative research plan) will specify that copies of all documents normally required by these regulations will be filed at the NAVMEDRSCHDEVCOM laboratory site. This provision is needed to ensure that the requirements of enclosure (1) for permanent storage of records will be met.

c. Microfiche copies are acceptable for permanent storage of all records.

d. Electronic media storage of experimental data initially recorded electronically is acceptable. Electronic media storage of original documents such as signed consent forms and records of CPHS action, however, is not currently acceptable. This restriction will remain in force until such time as documents stored by these methods may be admitted as evidence in legal proceedings. The research protocol should clearly state how electronically stored data will be validated and protected.

e. A copy of each research volunteer’s consent form will be filed in the research volunteer’s medical or dental records as directed in enclosure (1), paragraph 14. The research volunteer’s medical records will also include sufficient documentation to: substantiate what was done to the research volunteer during the research; clearly identify, by name or code, any drugs administered, and whether these drugs were investigational; identify investigational procedures performed; and identify significant obser-

vations, including any adverse effects. A specific notation of the existence and location of the experimental protocol and associated documents will be entered into the research volunteer's personal medical record. Entries into U.S. military medical and dental records are to be boldly labeled:

- DO NOT REMOVE -
THIS DOCUMENT REQUIRED TO BE PERMANENTLY FILED IN MEDICAL/DENTAL RECORD IN ACCORDANCE WITH SECNAVINST 3900.39B

In the event the research volunteer does not have a formal medical or dental record, the research records will be provided to the volunteer or the volunteer's health care provider for retention.

f. The Committee for the Protection of Human Subjects Recommendation (enclosure (11)), with original signatures of the voting Committee members, the convening authority and the approving authority, will be returned to the performing NAVMEDRSCHDEVCOM site after action is taken by the approving authority. This document will be permanently maintained in the research protocol.

g. Each convening authority will maintain a centralized system to record participation of all research volunteers in research protocols. This system will include:

(1) A centralized computer database at the performing NAVMEDRSCHDEVCOM activity in which will be recorded:

(a) identification of research protocol by name, unique research protocol number, Work Unit number, status of protocol (pending, active or complete) and list of all investigators;

(b) standardized identification of the research volunteers participating in the protocol (e.g. Social Security Number, if available);

(c) inclusive dates of participation of the research volunteer in the protocol.

(2) A centralized repository at the performing NAVMEDRSCHDEVCOM activity in which, at the completion of the research, will be stored:

(a) the original approved protocol with all approved modifications;

(b) all documents related to review for protection

of research volunteers from research risks, including correspondence;

(c) all original signed consent forms;

(d) other documents bearing original signatures;

(e) a 2-5 page executive summary of the research protocol including the research objectives, what was done, and the scientific results that were obtained;

(f) for each individual volunteer, a brief summary of the experimental exposure, the results obtained, and a complete description of all untoward events, including all diagnoses, treatments and final outcomes. [N.B. This material may be identical to the medical record entry.]

(3) An individual research volunteer file may be maintained for each volunteer during the time of participation in the protocol. The contents of this file are to be determined by the principal investigator. Disposition of the documents will be described in the protocol and be considered by the CPHS during the processes of initial and continuing review. If desired, a permanent individual file may be established and maintained. Such permanent individual files may include reports of research related physical, laboratory and other medical examinations and a chronologic history of participation in studies. Such files may be useful when individuals are assigned to commands as research subjects.

h. The CPHS will review these record maintenance elements of the research protocol with great care and thoroughness. The maintenance of such records will be a matter of primary concern during program review or inspection.

i. Approving authorities are required to keep a log of research protocols which they have approved. This log and the approval process will be subject to inspection by NAVMEDRSCHDEVCOM and higher authorities.

15. <u>Continuing Review of Research by the Committee for Protection of Human Subjects</u>.

a. The CPHS will review work conducted under previously approved research protocols at least annually as required by enclosure (1), paragraph 10.d.. This review will take place more frequently if the CPHS believes that more frequent review is indi-

cated.

b. The CPHS review will monitor and evaluate the following items: untoward events, complications, or injury to research volunteers; adequacy of medical care rendered; adequacy of the consent form and procedures for obtaining informed voluntary consent; the number of research volunteers studied; information developed during the research; faithfulness of research and safety procedures to the information upon which the CPHS's approval recommendation was based; qualifications of personnel; non-compliance with this instruction, related references, or other direction; completion of all required documents; maintenance of records and any other relevant information required by the CPHS. In documentation of CPHS review, a statement concerning the method of verification of information will be included. The format for the recommendation of the CPHS upon continuing review of the research is provided as enclosure (12).

c. If an investigator is added to the research effort after submission of the initial research protocol and initial Investigator Assurance Agreement, a Supplemental Investigator Assurance Agreement will be prepared and signed. A copy of the supplemental Investigator Assurance Agreement with the signature of the new investigator will be submitted in a timely manner to the CPHS and forwarded to the convening and approving authorities. The original will be incorporated into Appendix B of the research protocol. The CPHS will apprise the convening and approving authorities of all changes in investigators and collaborating institutions.

(1) Inclusion of an individual's name as an author on a formal report, manuscript or other document for publication or presentation indicates investigator status for that individual. If an Investigator Assurance Agreement signature has not been obtained for that investigator, the principal investigator is required to provide written explanation to the CPHS why the Investigator Assurance Agreement has not been completed, and the reason(s) for approval of the inclusion of the individual investigator as an author.

(2) The CPHS may recommend, and the convening or approving authority may require, removal of an investigator's name as an author on any presentation, report or publication if it is determined that:

(a) the principal investigator was negligent in obtaining and submitting a completed Investigator Assurance Agreement from the investigator in a timely manner; or

(b) if the investigator participated in research utilizing research volunteers, identifiable volunteer data or identifiable specimens from volunteers prior to completing the Investigator Assurance Agreement.

d. Whenever a protocol involving a collaborating institution is reviewed by that institution, the result of the review will be forwarded to the cognizant NAVMEDRSCHDEVCOM CPHS. The CPHS of the collaborating institution will perform such reviews at least annually. More frequent review may be required by the NAVMEDRSCHDEVCOM CPHS or the CPHS at the collaborating institution, as appropriate. Review by collaborating institutions will include, at least, the elements required in paragraph 16.b. above.

e. The CPHS will not allow any significant deviations from the approved research protocol unless the change is reviewed by the CPHS and approved in advance by the same authority who approved the original research protocol. The CPHS will report unauthorized deviations to the convening and approving authority, and make recommendations regarding whether or not it is necessary for the convening or approving authority to direct cessation of the research activity, initiate investigation into the infraction, or take other action.

f. In the course of continuing review of a research protocol, the CPHS may withdraw or modify its recommendation for approval. The CPHS may recommend suspension or termination of the research protocol if the current balance of risk to research volunteers versus benefit from the study is judged sufficiently unfavorable or uncertain, or if investigators do not comply with requirements for protection of research volunteers. In such cases, this change in recommendation will be accompanied by justification, endorsed by vote of Committee members, and forwarded to the convening and approving authorities for action. The format for the recommendation of the CPHS upon continuing review of the research is provided as enclosure (12).

(1) Recommendation for suspension or termination, and the rationale, will be reported to the principal investigator, the Commanding Officer of the activity convening the CPHS, the approving authority, NAVMEDRSCHDEVCOM and all other addressees in the approval chain.

(2) The CPHS may recommend removing the suspension once all deficiencies have been resolved.

(3) A termination can be reversed only by treating the study as a new research protocol submitted for complete review and approval.

16. Reporting Complications. Performing activities must notify NAVMEDRSCHDEVCOM and the research approving authority (if other than NAVMEDRSCHDEVCOM) by message or facsimile within 24 hours of any incident, accident, untoward drug reaction, appearance of disease or injury which may have occurred, or which could reasonably have occurred, as a result of using research volunteers in research. Telephone communication should also be used in addition to the above if the responsible individual believes faster notification is indicated.

a. Any complication or problem, including adverse reactions to biologics, drugs, radioisotopes, medical devices, or procedures, must be reported without delay to the principal investigator and the medical monitor, and to the cognizant Commanding Officer by any individual who detects the problem.

b. Unless outlined differently in the research protocol, the most senior military member and civilian staff member present will take whatever immediate action they consider necessary to protect research volunteers. Their actions, and the medical or dental treatment provided the research volunteer, will be reported directly to the Commanding Officer or Officer in Charge of the laboratory responsible for the study. The Commanding Officer or Officer in Charge will simultaneously notify the CPHS and all addressees in the approval chain of the research protocol.

c. As soon as possible, the CPHS will convene to consider the report and to advise the convening and approving authorities regarding whether the study should be continued, suspended or terminated. The recommendations of the CPHS will be forwarded to the convening and approving authorities and NAVMEDRSCHDEVCOM without delay.

17. Other Reporting Requirements.

a. The Director, Environment and Life Sciences, Office of the Director, Defense Research and Engineering, requires prompt reports, via NAVMEDRSCHDEVCOM, of:

(1) any unanticipated problems involving risks to research volunteers;

(2) any serious or continuing noncompliance with require-

ments for protection of human research volunteers; or

(3) any suspension or termination of CPHS recommendation for approval of research.

b. Commanding Officers are required to inform NAVMEDRSCHDEVCOM of the approval of any research protocol for which they are the approving authority (i.e., minimal risk research). A copy of the protocol including the CPHS Recommendation Document (enclosure (11)) is to be forwarded at the time of approval of the protocol. NAVMEDRSCHDEVCOM will maintain oversight of minimal risk research protocols in accordance with its responsibility to monitor compliance with Navy policy.

c. Compliance with reference (e) is required if investigators propose to administer questionnaire surveys. Information is required for all proposals that involve the administration of a paper-and-pencil questionnaire that asks the respondent for any biographical, health, occupational, attitudinal or similar information that is not part of an official service record. Compliance with this instruction does not pertain to questionnaire surveys involving Marine Corps personnel, but is applicable to work in which surveys are administered to Navy personnel, dependents (either Navy or Marine Corps), civil servants, or any other civilian personnel. A copy of a completed report form (OPNAV 5214/10) should be included in the protocol. Special care should be taken in the proposal to demonstrate that the questionnaire survey will provide worthwhile data, and that the survey has not been administered previously by other investigators under these same circumstances. Approval by CNO (OP-01) is required for a questionnaire survey to be administered.

d. The reports contained in this instruction are exempt from reports control by SECNAVINST 5214.2B.

18. Privacy Act Statements. All research volunteers who are either citizens of the United States or legally admitted aliens must be provided with a Privacy Act statement. The Privacy Act statement information may be provided in the text of the consent form, or as a separate statement attached to the consent form. Research volunteers are not required to sign a specific Privacy Act statement. The Privacy Act does not apply to foreign national research volunteers unless they are legally admitted to the United States. If a Privacy Act statement is not used in obtaining voluntary informed consent because the research volunteer is an alien not legally admitted to the United States, it is recommended that the concepts included in the Privacy Act statement be incorporated into

the text of the consent form. A sample Privacy Act Statement is provided as enclosure (9). This may be modified as appropriate.

19. Additional Study Standards. Requirements for specific types of research are found in the appendices of this instruction. They are:

a. Appendix - A: Research Involving Investigational Drugs, Biologics or Devices.

b. Appendix - B: Research Involving the Unlabeled Use of Drugs or Biologics.

c. Appendix - C: Research Involving Testing of Research Volunteers Suspected to be Infected with the Human Immunodeficiency Virus.

d. Appendix - D: Research Involving Physiological Stress.

20. NAVMEDRSCHDEVCOM Investigators Acting as Consultants.

It is recognized that NAVMEDRSCHDEVCOM personnel have scientific expertise which may lead to these personnel being sought out as consultants. The policy for NAVMEDRSCHDEVCOM personnel participating as a consultant for research involving research volunteers and conducted by another agency or institution is as follows:

a. Participation in the scientific community as a consultant is encouraged.

b. In cases where NAVMEDRSCHDEVCOM personnel act as consultants, they are required to assess the scientific, ethical and moral issues and conduct of the study for which they are consulted, and ensure that the study is scientifically sound, complies with all applicable regulations, and that the protection afforded research volunteers is in accordance with Navy policy.

c. NAVMEDRSCHDEVCOM personnel acting as consultants will not have substantial participation in the research in question. Substantial participation is demonstrated if the degree of involvement in the design, conduct, analysis, or reporting of the study is such that it will lead to co-authorship. This degree of participation indicates co-investigator status and requires full compliance with all regulations pertaining to the protection of research volunteers, and review of the research protocol in accordance with this instruction.

d. Use of Navy resources to support research, including the use of funds, technical personnel, laboratory facilities, equipment, supplies or capabilities, is considered investigator participation in the research. Such research requires review and approval in accordance with enclosures (1) through (5) and references (a) through (c).

e. Participation of NAVMEDRSCHDEVCOM personnel as consultants on research protocols involving research volunteers requires the approval of the Commanding Officer or Officer in Charge of the parent activity of the consultant.

f. These policies also apply to the case where personnel from other institutions participate as consultants to NAVMEDRSCHDEVCOM projects. In all non-exempt research, if there is substantial participation in the research on the part of the non-NAVMEDRSCHDEVCOM individual (as noted in paragraph 20.c.), co-investigator status exists and completion of the Individual Assurance Agreement and documentation of institutional review is required.

21. Restriction on Expenditure of Funds for Unapproved Research Involving Research Volunteers. Without the required approval for a research protocol involving research volunteers, NAVMEDRSCHDEVCOM Commanding Officers and Officers in Charge are directed that:

a. Funds may not be obligated or expended to:

(1) Enroll research volunteers in a study, acquire data, analyze data, or test specimens from research volunteers.

(2) Present research information by publication, submission for publication, presentation at meetings, or other means.

(3) Fund travel for the purpose of conducting the research protocol or for activities directly related to the participation of research volunteers.

(4) Fund any other activities for which approval of the research protocol for participation of research volunteers is required.

b. Preliminary activities normally required for the planning and implementation of a study, prior to active participation or enrollment of research volunteers in a specific protocol, are permissible.

c. A research protocol involving research volunteers that is

administratively suspended upon the recommendation of the CPHS for failure to meet the requirements of this instruction or enclosures (1) through (5) and references (a) through (c) will be considered to be unapproved.

d. The restriction on use of funds does not apply to meeting existing payrolls for employees or contractors who have been hired under previously existing approved research protocols. Under these circumstances, no new employees may be hired, or contractual obligations made, without the approval of NAVMEDRSCHDEVCOM.

e. Purchase of general purpose equipment and supplies (not related to a specific unapproved research protocol) and travel for administrative support of ongoing research activities (not specifically related to an unapproved protocol requirement) is permitted.

f. Investigators are not authorized to present research information either by publication, submission for publication, or presentation at meetings, unless the research protocol under which the information was collected or analyzed has specific approval.

g. Requests for waiver of this requirement, that are based on unusual extenuating circumstances, clearly demonstrated to meet the needs of the Navy and that do not place research volunteers at risk, are to be forwarded to NAVMEDRSCHDEVCOM for review.

h. It is expected that, due to the potentially significant adverse consequences of suspension of funding authority, all involved will act to resolve deficiencies in an expedient and professional manner, such that this restriction will be pertinent only in extreme circumstances.

22. Waiver of Requirements. Although it will be the rare exception, circumstances may exist wherein the best interest of the research volunteer is served by waiver of one or more of the requirements of this or other regulations. Requests for waiver should be submitted, using the chain of command, to the authority establishing the requirement or to the authority specifically authorized to waive the requirement. A recommendation for approval of the request for waiver by the CPHS, the convening authority, and by each echelon in the chain of command is required. Failure to obtain these recommendations for approval will result in disapproval and return of the request to the originator.

23. Authorization to Initiate Research Involving Research Volunteers. Research involving human volunteers requires compliance with this instruction and higher guidance. Investigators may en-

roll volunteers upon receipt of both final approval of the research protocol, as evidenced by the approval document (enclosure (11)), and the authorization to initiate the research granted by the Commanding Officer, Officer in Charge, or cognizant contractor official of the performing NAVMEDRSCHDEVCOM or contractor activity.

24. Action. This instruction is effective immediately. All NAVMEDRSCHDEVCOM personnel conducting research involving human research volunteers will comply with the provisions contained herein. Convening authorities will ensure that provisions are made for meeting space and sufficient administrative staff to support the review and record keeping duties of the CPHS.

E. T. FLYNN

Distribution:
Lists A & B

APPENDIX - A

Research Involving Investigational Drugs, Biologics or Devices

Use of investigational drugs, biologics or devices requires compliance with enclosure (4). In addition:

1. If a research protocol involves the use of investigational drugs, biologics or devices, approval by both NAVMEDRSCHDEVCOM and the Naval Investigational Drug Review Board is required, regardless of whether or not the protocol is reviewed by another body normally having authority to grant approval for such protocols. If the study is conducted outside the United States, approval of the host country government is also required.

2. In the event that an agreement exists for review and approval of research by a collaborating institution, the agreement is considered void for the purpose of this class of investigation, unless the agreement specifically pertains to the exact investigational product and exact research protocol under review.

3. If a research protocol involves the testing or use of a drug, biologic or device in human research that either (1) is not commercially available in the United States or (2) is produced or manufactured in a foreign (non-U.S.) facility, the product must be specifically described in the protocol.

a. Commercially available laboratory diagnostic equipment and devices are excluded from description provided the purpose of the research does not include testing of the equipment or device itself.

b. Drugs, biologics and devices that are produced or manufactured in foreign facilities, but are also approved or licensed by the U.S. Food and Drug Administration (FDA) for sale in the U.S. must be identified in the research protocol.

c. Drugs, biologics and devices that are produced or manufactured in foreign facilities, but are not approved or licensed by the FDA for sale in the U.S. are considered investigational and will require compliance with enclosure (4). This applies whether or not the product is used for an indication and in a dosage regimen that is accepted for the same generic compound produced in a FDA approved process.

4. Supplementation of an existing Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) with a new research protocol is desirable. This requires concurrence of the current responsible individual (holder of the IND or IDE) and approval by the FDA.

APPENDIX - B

Research Involving the Unlabeled Use of Drugs and Biologics

Any deviation from the indications, dose, route of administration, dosage form or treatment population of a drug, biologic or device approved or licensed by the U.S. Food and Drug Administration (FDA) is considered an unlabeled use. The following comments pertain:

1. Provided that the route of administration and the dosage form are not changed, a physician may modify an approved dosage regimen of an approved drug for treatment of individual patients. In cases where treatment of a disease or malady is the purpose of the modification, this unlabeled use is considered the “practice of medicine” and is not regulated by the FDA. The physician treating the patient bears the increased liability for the consequences of any deviation from accepted therapy.

2. If the purpose is not treatment of an individual patient, but rather a scientific study using research volunteers, this is considered research and not the “practice of medicine”. Such activi-

ties are regulated by the FDA and usually require filing of an IND and compliance with enclosure (4).

a. Unlabeled use of approved drugs or licensed biologics will require either an IND or documentation issued by the FDA of exemption from requirements for an IND. Similar requirements apply to devices.

b. If the research involves study of an approved drug or licensed biologic purchased or provided from an approved source with only a minor modification in dosage or indication, the primary issue in review by the FDA will be safety. In such cases, expedited processing and waiver of the usual 30 day review period at the FDA may be requested.

c. If the research meets the criteria of enclosure (5), the proposed use may be exempt from the requirement for an IND. The criteria used by the FDA in determining eligibility for an exemption are:

(1) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(2) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product , the investigation is not intended to support a significant change in the advertising for the product;

(3) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risk (or decreases the acceptability of the risks) associated with the use of the drug product;

(4) The investigation is conducted in compliance with the requirements for institutional review and voluntary informed consent; and

(5) The investigation is conducted in compliance with the restrictions on promotional sale of an investigational drug.

3. In <u>all</u> cases involving the use of an approved drug or licensed biologic for an unlabeled indication, the research will be considered greater than minimal risk and:

a. The principal investigator will request from the FDA and provide to the CPHS a document indicating exemption from the requirement for Investigational New Drug Application (IND).

b. The consent form will clearly state:

(1) an approved drug or licensed biologic is being used for an unlabeled indication;

(2) what is the variance from the labeled indications and proposed usage; and

(3) an explanation of reason for the unlabeled use.

APPENDIX - C

Research Involving Testing of Research Volunteers Suspected to be Infected with the Human Immunodeficiency Virus

The following comments pertain to research protocols involving testing of research volunteers for infection with the human immunodeficiency virus (HIV), and whose test results can be associated with personal identifiers (i.e. are not anonymous):

1. Research volunteers must be told in advance that they will be tested for infection with HIV, and that this information will be reported to them and to the appropriate military or civilian authorities if required by law or regulation. These statements are to be incorporated into the informed consent process.

2. Research volunteers must be told that the investigators are obligated to make test results available to the individual research volunteer. If a research volunteer does not want to know his or her result, his or her only recourse is not to participate in the study (reference (d)).

3. If a research volunteer is informed that he or she has tested positive for infection with the HIV, the investigators are obligated to ensure that the research volunteer is provided with the opportunity for appropriate counseling about the disease and infectivity.

4. If research volunteers are foreign nationals and research is conducted under the auspices of a host government, it remains the responsibility of NAVMEDRSCHDEVCOM investigators to ensure that

research volunteers are informed of their positive test result and provided the opportunity to receive appropriate counseling. Delegation of either of these responsibilities to host country officials, without participation of NAVMEDRSCHDEVCOM investigators in the process such that investigators could verify that the ethical and legal responsibilities of the NAVMEDRSCHDEVCOM investigators have been properly executed, is prohibited. This policy does not require NAVMEDRSCHDEVCOM investigators to personally and exclusively inform and counsel research volunteers, nor does it preclude appropriate delegation of these responsibilities. This policy does require that NAVMEDRSCHDEVCOM investigators participate in the process to the extent that they can verify that their research volunteers are being appropriately informed and counseled.

5. One of the greatest potentials for harm to a research volunteer involves disclosure of the confidential information regarding the research volunteer's HIV positive status. Considerations for protection of data and confidentiality are of particular importance in research involving research volunteers with HIV infection. These considerations and safeguards must be fully disclosed in the research protocol and consent form.

APPENDIX - D

Research Involving Physiological Stress

The following comments pertain to studies conducted at, by, or in collaboration with NAVMEDRSCHDEVCOM activities or by contractors funded by NAVMEDRSCHDEVCOM or its subordinate activities.

1. Studies are considered greater than minimal risk if they are designed to either increase heart rate to more than 70% of predicted maximal heart rate or oxygen consumption to more than 70% of predicted maximal oxygen consumption. These studies require:

a. A completely equipped "emergency cart" is to be immediately available at the site where the research volunteer undergoes the experimental stress. This "emergency cart" is to be properly stocked and maintained as directed by the Commanding Officer, Officer in Charge, or cognizant officer of the performing NAVMEDRSCHDEVCOM or contractor activity, and is to include equipment and drugs necessary to provide advanced cardiac life support. At a minimum there will be: capability to intravenously administer emergency cardiac drugs; equipment for endotracheal intubation and controlled ventilation with 100% oxygen; equipment to monitor and record cardiac rhythm; and equipment to electrically convert abnor-

mal cardiac rhythms.

b. A qualified medical officer (or civilian physician), currently certified in Advanced Cardiac Life Support, must be readily available during the entire study. The criteria that constitute reasonable proximity to the site of the experimental exposure are to be specified in the research protocol and approved by the reviewing CPHS.

c. At the beginning of the study, the medical officer (or civilian physician) will approve initiation of the study for each research volunteer. At the conclusion of the study, the medical officer (or civilian physician) will clear each research volunteer for release and resumption of normal activities.

d. At least one member of the research team will be continuously with the research volunteer from the beginning of the study until the research volunteer is released by a medical officer (or civilian physician). This research team member is required to have, at least, current "Basic Life Support" certification. Appropriate advanced medical training is strongly encouraged.

2. In all research involving significant physiological stress to research volunteers, specific criteria for termination of an individual research volunteer's participation in the experiment will be stated in the protocol and reviewed by the CPHS. Criteria for cessation of experimental exposure and an emergency treatment plan for any reasonably expected untoward event will be fully described in the protocol and readily available at the site of the experimental exposure.

FORMAT FOR NAVMEDRSCHDEVCOM HUMAN RESEARCH PROTOCOLS

(Principal Investigator Cover Letter to be Attached)

I. COVER PAGE(S)

1. Protocol Number [e.g. NSMRL 93-07 (Laboratory Name, Fiscal Year, Sequential Number)]
2. Title
3. Date of Submission
4. Approved Work Unit Title and Number

5. Principal Investigator (Name, title, institutional affiliation)

6. Co-Investigator(s) (Name, title, institutional affiliation)

7. Primary Performing Institution(s)

8. Collaborating Institution(s)

II. SIGNATURE PAGE(S) (Include typed name and title)

1. Principal Investigator

2. Co-investigator

3. Medical Monitor

4. Key Support Personnel

5. Division Head

6. Department Head

7. Scientific Director / Chief Scientist (as appropriate) (As verification of completion of review and recommendation for approval by the Scientific Review Committee - or equivalent)

8. Commanding Officer / Officer in Charge / Contractor Official of Performing Activity
(This signature indicates all necessary approvals have been obtained and final approval to initiate research

is given. This signature space should only be signed when the research is commencing. This is not to be used as a place to endorse the action of the Scientific Review Committee, Committee for the Protection of Human Subjects, or to signify official action as the convening or approving authority of a protocol.)

III. RECORD OF CHANGES TO THE PROTOCOL

IV. TABLE OF CONTENTS (Include Page Numbers)

V. SCIENTIFIC BACKGROUND AND OBJECTIVES

1. Background

2. Objectives

a. Hypothesis(es) to be tested

b. Other objective(s)

VI. EXPERIMENTAL METHODS (May be supplemented by appendices)

1. Experimental Procedures and Rationale

2. Sample Size Determination with Statistical Power Calculation (if indicated)

3. Justification for Exclusion of Specific Groups

4. Required Equipment and Supplies (as needed to ensure proper coordination of research effort)

VII. ORGANIZATION OF RESEARCH EFFORT

1. Duties and Responsibilities

2. Chain of Command

VIII. RISKS AND DISCOMFORTS TO RESEARCH VOLUNTEERS

1. Risk to the Volunteer and Means of Mitigation

2. Special Risks to Pregnant or Potentially Pregnant Women Volunteers

3. Safety Precautions and Emergency Procedures

4. Assessment of Sufficiency of Plans to Deal With Untoward Events or Injuries

5. Qualification of Medical Monitor and Medical Support Personnel

IX. DESCRIPTION OF THE SYSTEM FOR MAINTENANCE OF RECORDS

1. Experimental Data

2. Research Protocol, Consent Forms, and Related Documents for Protection of Human Research Volunteers

3. Individual Medical Records

X. APPENDICES (If not applicable, state “N/A”)

A. Sample of Consent Document(s) and Privacy Act Statement Used

B. Completed Investigator Assurance Agreement(s)

C. Review for Protection of Human Research Volunteers from Research Risks

1. Recommendation(s) of the Committee for the Protection of Human Subjects (CPHS)

2. Minutes of the Meeting of the CPHS

a. Summary of discussion

b. Anonymous statement(s) describing the reason(s) for a vote to disapprove or abstain from voting

3. Recommendation of the Convening Authority

4. Action of the Approving Authority

5. Other documentation (as required)

a. Unlabeled use of approved drugs or licensed biologics

Provide documentation from the Food and Drug Administration (FDA) authorizing exemption from

the requirement for Investigational New Drug Application (IND)

b. Experimental drugs, biologics or devices

(1) Documentation of an approved IND or Investigational Device Exemption (IDE) from the FDA

(2) Approval of the Naval Investigational Drug Review Board (NIDRB)

c. Documentation of review and action taken by all collaborating institution(s)

(1) Acceptable results of review are: approval, exemption from review, joint review or other formal review agreement

(2) Certification by the principal investigator that protocol submitted for review is the same final copy approved or under simultaneous review by collaborating institution(s)

d. Host Government Approval if Research is Performed in a Foreign Country

e. Legal Issues

(1) Sufficiency of third party permission

a. Citation of statutory authority

b. CPHS determination regarding requirement for assent

(2) Citation of statutory authority for compensation of volunteers

(3) Other

f. OPNAV Form 5214-10 (if required for questionnaire survey - include CNO approval document)

g. Request for waiver of requirement(s) for protection of human research volunteers

h. Documentation of exemption from compliance with regulations for the protection of human research volunteers (State authority and criteria for exemption)

i. Other

D. POST APPROVAL DOCUMENTATION

1. Change of investigator(s), medical monitor or collaborating institution(s) (Addition or deletion)

2. Significant modification(s) to the protocol

4. CPHS continuing review (At least annually)

a. Review by NAVMEDRSCHDEVCOM activity

b. Review by collaborating institution(s)

c. Modification of CPHS recommendations

5. Documentation of all official action since initial submission and review

E. SPECIAL REPORTS

1. Unanticipated complications or problems

2. Reports of non-compliance with requirements for protection of human research volunteers

3. Adverse CPHS action

a. Recommendation for suspension

b. Recommendation for termination

4. Resulting action by convening and approving authorities

F. - Z. AS NEEDED

SAMPLE CONSENT FORM - MODIFY AS APPROPRIATE

TITLE OF PROTOCOL
VOLUNTARY CONSENT TO PARTICIPATE

(USE CONTENT OF PARAGRAPHS 1 - 7 FOR ALL STUDIES)

1. You are being asked to volunteer to participate in a research study entitled "_____". The purpose of this study is _____. You will be asked to participate from date to date, or a total of inclusive time interval. There will be approximately _____ volunteers participating in this study. During your participation in this study, you will be involved in the following procedures or tests: _____, _____, _____, etc.. Of these procedures, _____ and _____ are considered routine and _____ is considered an experimental procedure.

2. The investigators believe that the risks or discomforts to you are _____.

3. The benefit(s) that you may expect from your participation in this research is _____.

4. Alternative procedures or courses of treatment which may be of benefit to you, instead of participating in the procedures or treatment(s) in this research study, are _____. The relative advantages and disadvantages of each are _____.

5. Your confidentiality during the study will be ensured by _____. The confidentiality of the information related to your participation in this research will be ensured by _____.

6. If you have questions about this study you should contact the following individuals: for questions about research (science) aspects contact investigator at ____; for questions about medical aspects, injury, or any health or safety questions you have about your or any other volunteer's participation, contact medical monitor at _____; for questions about the ethical aspects of this study, your rights as a volunteer, or any problem related to protection of research volunteers, contact Chairperson or designee of CPHS at _____; and for questions about _____ contact _____ at _____.

7. Your participation in this study is completely voluntary. If you do not want to participate, there will be no penalty and you will not loose any benefit to which you are otherwise entitled. You may discontinue your participation in this study at any time

you choose. If you do stop, there will be no penalty and you will not loose any benefit to which you are otherwise entitled.

Encl (8)

TITLE OF PROTOCOL

(IF THE STUDY INVOLVES GREATER THAN MINIMAL RISK)
(USE CONTENT OF PARAGRAPHS 8 - 15)

8. If injury occurs as a result of your participation as a volunteer in this research project, compensation in the form of _____ may be available to you. Medical care available to you is _____. You may obtain further information about these issues from _____.

9. The treatment or procedure may involve risk to you that are presently unforeseeable. If you are pregnant or become pregnant, there may be additional risks to you, or to the embryo or fetus you are carrying, which are presently unforeseeable.
(N.B. See NMRDCINST 3900.2 for additional specific requirements and guidelines).

10. Your participation in this study may be stopped by the researchers or the medical monitor without your consent. The anticipated reasons that would make this necessary are _____.

12. Additional costs to you that may result from your voluntary participation in this study are _____.

13. If you decide to withdraw from further participation in this study, it is expected that _____. In order to ensure your safe and orderly withdrawal from the study, we ask that _____. Again, we would like to tell you that you may discontinue your participation in this study at any time you choose and without penalty. (Continue with the following, if necessary) Abruptly stopping your participation in this study (may or will be) harmful to you, therefore, when you inform us that you want to stop, the following procedures will be followed: _____.

14. Major new findings developed during the course of the research, which may relate to your willingness to continue participation, will be provided to you.

15. Official government agencies, such as _____, may have a need to inspect the research records from this study, including

yours, in order to fulfill their responsibilities.

(FOR ALL STUDIES INVOLVING U.S. NATIONAL VOLUNTEERS)
(USE CONTENT OF PARAGRAPH 16)

16. I have received a statement informing me about the provisions of the Privacy Act.

TITLE OF PROTOCOL

(USE CONTENT OF PARAGRAPHS 17 & 18 FOR ALL STUDIES)

17. I have been informed that _____ is responsible for storage of my consent form and the research records related to my participation in this study. These records are stored at _____.

18. I have asked the questions on the attached paper, and the written answers provided by the researcher(s) are understandable to me and are satisfactory. I understand what has been explained in this consent form about my participation in this study. I (do / do not) need further information to make my decision whether or not I want to volunteer to participate. By my signature below, I give my voluntary informed consent to participate in the research as it has been explained to me, and acknowledge receipt of a copy of this form for my own personal records.

(REQUIRED FOR ALL STUDIES)

_____ _____
Volunteer Date (DD/MM/YY)

_____ _____
Witness Date (DD/MM/YY)

_____ _____
Investigator Date (DD/MM/YY)

[N.B. Attach Privacy Act Statement if required and not included in the text of the consent form]

SAMPLE PRIVACY ACT STATEMENT

(Format May Be Modified As Necessary)

1. Authority. 5 U.S.C. 301

2. Purpose. Medical research information will be collected in an experimental research project entitled "(State Name of Research Protocol)" to enhance basic medical knowledge, or to develop tests, procedures, and equipment to improve the diagnosis, treatment, or prevention of illness, injury, or performance impairment.

3. Routine Uses. Medical research information will be used for analysis and reports by the Departments of the Navy and Defense, and other U.S. Government agencies. Use of the information may be granted to non-Government agencies or individuals by the Navy Surgeon General following the provisions of the Freedom of Information Act or contracts and agreements. I voluntarily agree to its disclosure to agencies or individuals identified above and I have been informed that failure to agree to this disclosure may make the research less useful. The "Blanket Routine Uses" that appear at the beginning of the Department of the Navy's compilation of medical data bases also apply to this system.

4. Voluntary Disclosure. Provision of information is voluntary. Failure to provide the requested information may result in failure to be accepted as a research volunteer in an experiment or removal from the program.

Attached: Consent statement for this experiment, signed by the research volunteer.

Encl (9)

INVESTIGATOR ASSURANCE AGREEMENT

I, the department head (or equivalent position), principal investigator or co-investigator, cited as responsible for performing and monitoring the research under the protocol entitled, "(State Number and Name of Research Protocol)", have read and understand the provisions of Title 32 Code of Federal Regulations Part 219 (Protection of Human Subjects), Department of Defense (DoD) Directive 3216.2 (Protection of Human Subjects in DoD-Supported Research), Secretary of the Navy Instruction (SECNAVINST) 3900.39B (Protection of Human Subjects), Naval Medical Command Instruction (NAVMEDCOMINST) 6710.4 "Use of Investigational Agents in Human Beings" - if applicable), and Naval Medical Research and Development Command Instruction (NMRDCINST) 3900.2 (Protection of Human Research Volunteers from Research Risks), SECNAVINST 5370.2H (Standards of Conduct) (and local instructions, as applicable). I will abide by all applicable laws and regulations, and agree that in all cases, the most restrictive regulation related to a given aspect of research involving protection of research volunteers will be followed. In the event that I have a question regarding my obligations during the conduct of this Navy sponsored project, I have ready access to each of these regulations, as either my personal copy or available on file from the Chairperson, Committee for the Protection of Human Subjects. I understand that my immediate resource for clarification of any issues related to the protection of research volunteers is the Chairperson, Committee for the Protection of Human Subjects.

Signatures and dates: (DD/MM/YY)

_____ __/__/__

(Typed Name)
Department Head

_____ __/__/__

(Typed Name)
Principal Investigator

_____ __/__/__

(Typed Name)
Co-Investigator

(Continue to include all investigators)

Encl (10)

COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS RECOMMENDATION

Date of Review: __/__/__ Protocol Number: _____

Approximate Dates of the Research - from: __/__/__ to: __/__/__

Title of Research Protocol: _____
Principal Investigator: _____
Work Unit Number: _____

In our opinion the research and safeguards described in the attached research protocol meet the standards set forth in DoD Directive 3216.2, SECNAVINST 3900.39B, and NMRDCINST 3900.2 (and local instructions, as applicable) - namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. Minutes of our deliberations concerning the review of this research protocol are attached, including anonymous statements giving reason(s) for non-concurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of __ for, __ against, __ abstaining, with __ members disqualified from review and __ members absent, we recommend to (circle only one response):

1. Approve, as research of no more than minimal risk (Attach detailed minor modifications needed - if any).
2. Approve, as research of more than minimal risk but not requiring ASN(RD&A) approval (Attach detailed minor modifications needed - if any).
3. Approve, as research requiring ASN (RD&A) approval (Attach detailed minor modifications needed - if any).
4. Return to principal investigator for specific revision before possible resubmission.
5. Disapprove (State Reason(s)).

The Committee recommends the first scheduled review on: __/__/__

COMMITTEE MEMBERS

Typed Name, Address & Representation	Signature	Date (DD/MM/YY)
_____	_____	__/__/__
Chairperson Name & Address		

- CONTINUED -

Encl (11)

COMMITTEE MEMBERS

(Continued)

Typed Name, Address & Representation	Signature	Date (DD/MM/YY)
Name, Address & Representation	_____	__/__/__
Name, Address & Representation	_____	__/__/__
Name, Address & Representation	_____	__/__/__
Name, Address & Representation	_____	__/__/__

Name, Address & Representation _____ __/__/__

Name, Address & Representation _____ __/__/__

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Name, Address & Representation _____ __/__/__

Name, Address & Representation _____ __/__/__

Name, Address & Representation _____ __/__/__

Name, Address & Representation _____ __/__/__

(Etc. for <u>all</u> appointed CPHS members - indicate on signature line if member is absent or is not allowed to participate due to conflict of interest.

****

RECOMMENDATION OF CONVENING AUTHORITY

1. I concur with the recommendation of the Committee for the Protection of Human Subjects (CPHS).

2. I concur with the recommendations of the CPHS, but recommend additional modifications or restrictions (Attach recommendations).

3. I disagree with the recommendation of the CPHS and recommend ... (Attach recommendations and reasons).

Typed Name & Title	Signature	Date (DD/MM/YY)
Name Title	_____	__/__/__

****

DETERMINATION OF APPROVING AUTHORITY

1. I concur with the recommendation of the CPHS and the Committee Convening Authority, and approve the research for a period of one year from the date below.

   First Review Required No Later Than: __/__/__

2. I concur with the recommendations of the CPHS and the Committee Convening Authority, but require additional modifications or restrictions prior to approval (Attach modifications or restrictions required).

   First Review Required No Later Than: __/__/__

3. I disagree with the recommendations of the CPHS or the Committee Convening Authority and recommend ... (Attach statement regarding recommendations and reasons).

Typed Name & Title	Signature	Date
Name Title	_____	__/__/__

COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS RECOMMENDATION

CONTINUING REVIEW

Date of Review: __/__/__ Protocol Number: _____

Date Research Started: __/__/__ No. of Previous Reviews: _____

Title of Research Protocol: _____
Principal Investigator: _____
Work Unit Number: _____

In our opinion the research and safeguards described in the attached research protocol have/have not meet the standards set forth in DoD Directive 3216.2, SECNAVINST 3900.39B, and NMRDCINST 3900.2 (and local instructions, as applicable) - namely, that the participation of humans as experimental research volunteers is limited to those situations in which voluntary informed consent is obtained; and that such participation is confined to research projects and clinical investigations which are necessary, scientifically sound, reasonably safe, and in which the benefit to be derived clearly justifies the risk incurred by the research volunteer. The report of the investigators submitted for review and the minutes of our deliberations concerning the review of this research protocol are attached, including anonymous statements giving reason(s) for nonconcurrence or abstention (if the recommendation of the committee is not unanimous).

By vote of __ for, __ against, __ abstaining, with __ members disqualified from review and __ members absent, we recommend to (circle only one response):

1. Continue the research.

2. Continue the research with minor modifications to the protocol (Attach detailed minor modifications needed).

3. Suspend the research (State reasons).

4. Terminate the research (State reasons).

The Committee recommends the next scheduled review on: __/__/__

COMMITTEE MEMBERS

Typed Name, Address & Representation	Signature	Date (DD/MM/YY)
_____	_____	__/__/__
Chairperson Name & Address		

- CONTINUED -

COMMITTEE MEMBERS

(Continued)

Typed Name, Address & Representation	Signature	Date (DD/MM/YY)
Name, Address & Representation	_____	__/__/__
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Name, Address & Representation	_____	__/__/__
Name, Address & Representation	_____	__/__/__
Name, Address & Representation	_____	__/__/__

(Etc. for all appointed CPHS members - indicate on signature line if member is absent or is not allowed to participate due to conflict of interest.

****

RECOMMENDATION OF CONVENING AUTHORITY

1. I concur with the recommendation of the Committee for the Protection of Human Subjects (CPHS).

2. I concur with the recommendations of the CPHS, but recommend additional modifications or restrictions (Attach recommendations).

3. I disagree with the recommendation of the CPHS and recommend ... (Attach recommendations and reasons).

Typed Name & Title	Signature	Date (DD/MM/YY)
Name Title	_____	__/__/__

****

DETERMINATION OF APPROVING AUTHORITY

1. I concur with the recommendation of the CPHS and the Committee Convening Authority, and approve the continued research for a period of one year from the date below.

   Next Review Required No Later Than: __/__/__

2. I concur with the recommendations of the CPHS and the Committee Convening Authority, but require additional modifications or restrictions prior to providing continuing approval (Attach modifications or restrictions required).

   Next Review Required No Later Than: __/__/__

3. I disagree with the recommendations of the CPHS or the Committee Convening Authority and recommend ... (Attach statement regarding recommendations and reasons).

Typed Name & Title	Signature	Date
Name	_____	__/__/__

Title